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Signed R. Mahoney

Dated 31 August 1999

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10) A use, composition or method according to anyone of claims 1 to 4, whereby predominant interaction at peripheral receptors is achieved by using a mGluR antagonist which does not substantially cross the blood-brain barrier.

11) A use, composition or method according to anyone of claims 1 to 4, whereby predominant interaction at peripheral receptors is achieved by administering the mGluR antagonist in such a way that it does not substantially penetrate the CNS.

12) A use, composition or method according to anyone of claims 1 to 4, whereby predominant interaction at peripheral receptors is achieved by administering the mGluR antagonist topically.

13) A use, composition or method according to anyone of claims 1 to 4, whereby predominant interaction at peripheral receptors is achieved by administering the mGluR antagonist transdermally.

14) A use, composition or method according to anyone of claims 1 to 13, whereby the condition to be treated is inflammatory pain.

15) A use, composition or method according to anyone of claims 1 to 13, whereby the condition to be treated is neuropathic pain.

Claims:

1) The use of a mGluR antagonist for the treatment of pain, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

2) The use of a mGluR antagonist in the manufacture of a pharmaceutical composition for the treatment of pain by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

3) A pharmaceutical composition incorporating as active agent a mGluR antagonist, for use in the treatment of pain, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

4) A method of treating pain in a subject in need of such treatment, comprising administration of a mGluR antagonist, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

5) A use, composition or method according to anyone of claims 1 to 4, whereby the mGluR antagonist acts at mGluR receptors of Group I and/or II.

6) A use, composition or method according to anyone of claims 1 to 4, whereby the mGluR antagonist acts at mGluR receptors of Group I.

7) A use, composition or method according to anyone of claims 1 to 4, whereby the mGluR antagonist acts at mGluR5 receptors.

8) A use, composition or method according to anyone of claims 1 to 4, whereby the mGluR antagonist is a specific mGluR5 antagonist.

9) A use, composition or method according to anyone of claims 1 to 4, whereby predominant interaction at peripheral receptors is achieved by using a mGluR antagonist which does not substantially penetrate the CNS.

Pharmazeutische Technologie 1st Edition, Springer and in GB 2098865 A or DOS 3212053, the contents of which are incorporated herein by reference.

Conveniently the composition is in the form of a viscous liquid, ointment or solid reservoir or matrix. For example the mGluR antagonist is dispersed throughout a solid reservoir or matrix made of a gel or a solid polymer, e.g. a hydrophilic polymer.

The active agent may be incorporated in a plaster.

The amount of mGluR to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of the mGluR antagonist, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required.

Analgesic effect achieved according to the invention is suitable for the treatment of pain of various genesis or aetiology, in particular in the treatment of inflammatory pain and associated hyperalgesia, neuropathic pain and associated hyperalgesia, chronic pain, e.g. severe chronic pain, post-operative pain and pain associated with various conditions including cancer, angina, renal or billiary colic, menstruation, migraine and gout.

Inflammatory pain may be of diverse genesis, including arthritis and rheumatoid disease, teno-synovitis and vasculitis. Neuropathic pain includes trigeminal or herpetic neuralgia, diabetic neuropathy pain, causalgia and deafferentation syndromes such as brachial plexus avulsion.

MGluR antagonists which can suitably be used according to the invention include the above defined compounds of formula I, as well as compounds described in Annoura et al., Bioorg. Med. Chem. Lett. 6(7), 763-766 (1996) and in EP 807621 A1, WO 9612715 A1 and USP 5,717,109, the contents of which are incorporated herein by reference.

mg/kg. Similar results may be achieved by using other mGluR antagonists as herein defined.

These findings indicate that the use for treating pain according to the invention is not limited to the treatment of inflammatory pain.

In accordance with the above, the present invention provides:

a) The use of a mGluR antagonist for the treatment of pain, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

b) The use of a mGluR antagonist in the manufacture of a pharmaceutical composition for the treatment of pain by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

c) A pharmaceutical composition incorporating as active agent a mGluR antagonist, for use in the treatment of pain, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

d) A method of treating pain in a subject in need of such treatment, comprising administration of a mGluR antagonist, whereby analgesic effect is achieved by interaction of said antagonist primarily or predominantly at peripheral mGluR receptors.

Preferably said analgesic effect is achieved exclusively or substantially exclusively at peripheral mGluR receptors.

Predominant interaction at peripheral mGluR receptors is preferably achieved by chosing an active agent which does not substantially penetrate the CNS or is administered in such a way that it does not substantially penetrate the CNS.

Modes of administration which are such that the administered mGluR antagonist does not substantially penetrate the CNS include topical, particularly transdermal administration.

For transdermal administration, the mGluR antagonist may be administered in any conventional liquid or solid transdermal pharmaceutical composition, e.g. as described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser,

obtained for glutamate receptor agonists: glutamate ~ 2-chloro-3-hydroxyphenylglycine (CHPG) > DHPG > NMDA > AMPA > (±)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY 314582) > L-4-phosphono-2-amino-butiric acid (L-AP4). Of the receptor selective compounds tested, those acting at Group I mGluRs were the most potent hyperalgesic agents.

These results demonstrate that the mGluR Group I receptors are particulary involved in nociceptive transmission and that they are expressed peripherally.

4. On co-administration of the mGluR Group I agonist DHPG to the rat hind paw in the same model as under 3, the mGluR5 antagonists dose-dependently inhibit the DHPG-induced hyperalgesia, while the mGluR Group I antagonist (S)-4-carboxyphenylglycine [(S)-4C-PG], which is selective for mGluR1 over mGluR5 receptors, has limited effect.

These results indicate that the mGluR5 receptor is particularly involved in nociceptive transmission and confirm that it is expressed peripherally.

The above findings indicate that hyperalgesia associated to inflammatory pain can be treated with mGluR antagonists, e.g. mGluR antagonists having a mGluR5 antagonistic component. Moreover they indicate that a mGluR antagonist which does not (or is administered in such a way that it does not) substantially act at central mGluR receptors, while being substantially free of central effects, will not be less active as to its anti-hyperalgesic activity than a mGluR antagonist which penetrates the CNS.

A further experiment using a model of neuropathic pain, was furthermore performed as described below:

5. Intraplantar administration of mGluR antagonists, e.g. acting at mGluR5 receptors, e.g. of specific mGluR5 antagonists, for example as defined above, dose-dependently reverses mechanical hyperalgesia in the rat partial sciatic nerve ligation model of neuropathic pain (Seltzer et al., Pain 43: 205-218, 1990). In this model, intraplantar administration of antagonists of formula I, for example, produces a significant reversal of mechanical hyperalgesia at doses of about 1 to about 100

Activity of mGluR antagonists in accordance with the present invention, in particular mGluR antagonists acting at Group I receptors, more particularly at mGluR5 receptors, e.g. selective mGluR antagonists, for example of formula I, in particular the above-mentioned compounds, can be demonstrated in a series of experiments indicative of usefulness in pain by interaction at peripherally expressed receptors.

A first group of experiments using models of persistent inflammatory pain was performed as described below:

1. Oral administration of mGluR antagonists, e.g. acting at mGluR5 receptors, e.g. of specific mGluR5 antagonists, for example as defined above, dose-dependently reverses mechanical hyperalgesia in the complete Freund's adjuvant rat model of inflammatory pain (Bartho et al., Naunyn Schmiedebergs Arch. Pharmacol. 342, 666-670, 1990). In this model, oral administration of antagonists of formula I, for example, produces a maximal reversal of between 60-95% reversal of inflammatory hyperalgesia with ED_{50}'s ranging between 4 and 25 mg/kg. The anti-hyperalgesic effects are of good duration (greater than 5 hours) and the onset is very rapid. Similar effects may be achieved by using other mGluR antagonists as herein defined.

   These results indicate that mGluR antagonists, e.g. mGluR5 antagonists, in particular selective mGluR5 antagonists, are useful in inflammatory pain.

2. On intracerebroventricular or intrathecal administration of the mGluR antagonists capable of penetrating the blood-brain barrier, e.g. specific mGluR5 antagonists in the same complete Freund's adjuvant rat model (Bartho et al., 1990 as above), the mGluR antagonists produce only weak anti-hyperalgesic effects.

   The brain and spinal cord sites are therefore unlikely to be the primary sites of action following oral administration.

3. In a naïve rat hind paw test of mechanical hyperalgesia (Randall and Seditto Arch. Int. Pharmacodyn, Ther. 111:409-419, 1957), the following rank order of potency is

$Y_2 - R_5$ (III)

in which one of Y_1 and Y_2 denotes a reactive esterified hydroxy group or an halogen such as bromine or iodine and the other one represents a group Y_3-C≡C- in which Y_3 is hydrogen or a metallic group, and R_1, R_2, R_3, R_4 and R_5 are as defined above and functional groups R_1, R_2, R_3 and R_4 as well as functional substituents of R_5 may be temporarily protected.

The reaction can be performed according to known methods, e.g. Heck coupling or Grignard. The starting materials are known or can be obtained from known materials using conventional methods.

It has been found that the compounds of formula I are useful as modulators of mGluRs, particularly as selective mGluR5 antagonists.

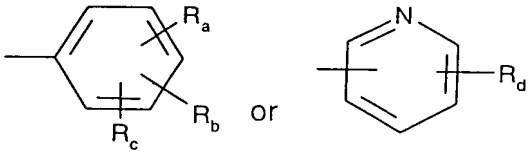
Modulation of mGluRs can be demonstrated in a variety of ways, inter alia, in binding assays and functional assays such as second messenger assays or measurement of changes in intracellular calcium concentrations. For example, measurement of the inositol phosphate turnover in recombinant cell lines expressing hmGluR5a showed, for the compounds of formula I, IC_{50} values of about 1nM to about 50μM.

In particular, the compounds of formula I exhibit a marked and selective modulating, especially antagonistic, action at human mGluRs, especially mGluR5. This can be determined in vitro for example at recombinant human metabotropic glutamate receptors, especially PLC-coupled subtypes thereof such as mGluR5, using different procedures like, for example, measurement of the inhibition of the agonist induced elevation of intracellular Ca^{2+} concentration in accordance with L. P. Daggett et al. Neuropharm. Vol. 34, pages 871-886 (1995), P. J. Flor et al., J. Neurochem. Vol. 67, pages 58-63 (1996) or by determination to what extent the agonist induced elevation of the inositol phosphate turnover is inhibited as described by T. Knoepfel et al. Eur. J. Pharmacol. Vol. 288, pages 389-392 (1994), L. P. Daggett et al., Neuropharm. Vol. 67, pages 58-63 (1996) references cited therein. Isolation and expression of human mGluR subtypes are described in US-Patent No. 5,521,297. The compounds showed IC_{50} values for the inhibition of the quisqualate-induced inositol phosphate turnover, measured in recombinant cells expressing hmGluR5a, of about 1nM to about 50 μM.

R_3 is hydrogen, (C_{1-4}) alkyl, carboxy, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbamoyl, hydroxy(C_{1-4})alkyl, di(C_{1-4})alkylaminomethyl, morpholinocarbonyl or 4-(4-fluoro-benzoyl)- piperidin-1-yl-carboxy,

R_4 is hydrogen, hydroxy, carboxy, (C_{2-5})alkanoyloxy, (C_{1-4})alkoxycarbonyl, amino (C_{1-4})alkoxy, di(C_{1-4})alkylamino(C_{1-4})alkoxy, di(C_{1-4})alkylamino(C_{1-4})alkyl or hydroxy(C_{1-4})alkyl, and

R_5 is a group of formula



wherein

R_a and R_b independently are hydrogen, halogen, nitro, cyano, (C_{1-4})alkyl, (C_{1-4})alkoxy, trifluoromethyl, trifluoromethoxy or (C_{2-5})alkynyl, and

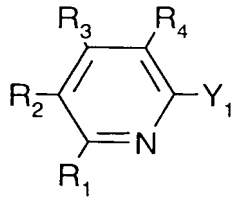
R_c is hydrogen, fluorine, chlorine bromine, hydroxy (C_{1-4})alkyl, (C_{2-5})alkanoyloxy, (C_{1-4})alkoxy or cyano, and

R_d is hydrogen, halogen or (C_{1-4})alkyl,

in free form or in form of pharmaceutically acceptable salts.

More particularly the findings are based on experiments performed with compounds including 2-[2-(pyridin-3-yl)ethenyl]-6-methyl-pyridine, 3-methoxy-6-methyl-2-m-tolylethynyl-pyridine, 2-methyl-6-(2,3,5-trichloro-phenylethynyl)-pyridine and 2-(3-fluoro-phenylethynyl)-6-methyl pyridine (used as free bases).

The compounds of formula I can be prepared by reacting a compound of formula II



(II)

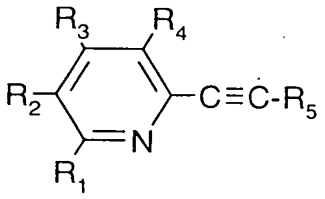
with a compound of formula III

mGluR group I agonist 3,5-dihydroxyphenylglycine (DHPG) induced an increase in spontaneous nociceptive responses in the rat (Fisher and Coderre, Neuroreport. 9:1169-1172, 1998). Further evidence for a spinal role of mGluR Group I receptors in nociceptive processing was indicated by the report of antinociceptive effects of intrathecally administered anti-rat mGluR1 and mGluR5 antibodies. Both of these antibodies reversed the spontaneous nociceptive responses evoked by intrathecal administration of DHPG (Fundytus et al., Neuroreport. 9:731-735, 1998). In addition, they both reversed the cold allodynia that developed following sciatic nerve injury in the rat, indicating that spinal mGluR1 and mGluR5 receptors may play a role in neuropathic pain.

All the available evidence based on the above-mentioned studies indicates that mGluR involvement in nociceptive processing is restricted to the CNS. Therefore, for analgesic efficacy, it would have been expected that therapy with mGluR antagonists would require access to the CNS, e.g. central administration or ability of the antagonist to pass the blood-brain barrier.

It has now surprisingly been found that the hyperalgesic effects of the mGluR antagonists are primarily mediated by peripherally expressed mGluR, particularly mGluR5, receptors.

These findings are based on experiments performed with a new class of compounds which display a high degree of selectivity and affinity as antagonists of the human and rat mGluR5 (specific mGluR5 antagonists). These are compounds of formula I



(I)

wherein

R_1 is hydrogen, (C_{1-4}) alkyl, (C_{1-4})alkoxy, cyano, ethynyl or di(C_{1-4})alkylamino,

R_2 is hydrogen, hydroxy, carboxy, (C_{1-4}) alkoxycarbonyl, di(C_{1-4})alkylaminomethyl, 4-(4-fluoro-benzoyl)-piperidin-1-yl-carboxy, 4-t.-butyloxycarbonyl-piperazin-1-yl-carboxy, 4-(4-azido-2-hydroxybenzoyl)-piperazin-1-yl-carboxy or 4-(4-azido-2-hydroxy-3-iodo-benzoyl)-piperazin-1-yl-carboxy,

Organic Compounds

The present invention relates to a new pharmaceutical use of compounds having antagonistic activity at metabotropic glutamate receptors (mGluRs).

Based on their amino acid sequence homology, agonist pharmacology and coupling to transduction mechanisms, the 8 presently known mGluR sub-types are classified into three groups. Group I receptors (mGluR1 and mGluR5) are linked to phosphoinositide (PI) hydrolysis. Group II (mGluR2 and mGluR3) receptors and Group III receptors (mGluRs 4, 6, 7 and 8) are negatively coupled to adenylyl cyclase.

Electrophysiological studies of mGluRs have demonstrated that their activation strongly contributes to synaptic modulation in the central nervous system (CNS). Pharmacological and physiological studies of the spinal cord reflex suggest that mGluRs can both attenuate or enhance the motor output of the spinal cord (see Boxall et al., Neuroscience, 82:591-602, 1998). Intracellular studies have revealed that membrane properties of wide dynamic range interneurons and ventral horn neurons of the spinal cord are also directly affected by mGluR activation (Morisset and Nagy, J. Neurophysiol. 76:2794-2798, 1996; Liu and King, Br. J. Pharmacology. 116,105P, 1995).

Molecular biological studies have confirmed the expression of RNA's for metabotropic glutamate receptors (mGluRs) in mammalian central nervous system (CNS). Receptor proteins have also been described in mammalian brain for mGluR1-5, mGluR7 and mGluR8 sub-types. These receptor subtypes appear to be localised on neurons both pre- and post-synaptically, and also appear in glial cells. The presence of mGluR mRNA in the adult rat spinal cord has been demonstrated using in situ hybridisation techniques (Boxall et al. 1998 - see above). mGluRs 1, 3-5 and 7 subtype mRNA's are expressed in the rat spinal cord. Furthermore, immunohistochemistry techniques have demonstrated the expression of mGluR5 protein in the human and rat spinal cord and in the rat dorsal root ganglion cells (Valerio et al., Neuroscience Research. 28:49-57, 1997).

In vivo electrophysiological studies have revealed that spinal cord mGluR activation contributes to the development of spinal hyperexcitability (see Boxall et al. 1998 for review). Behavioural pharmacological studies in rats indicate that the intrathecally administered

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Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application

B.A. Yorke & Co

Signature: B.A. Yorke & Co. Date: 02.10.98

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. E. Cheetham** **0181 560 5847**

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1/77

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1.	Your reference	4-30652/P1
2.	Patent application number *(The Patent Office will fill in this part)*	02 OCT 1998 **9821503.1**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125457002
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
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